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Myocardial infarction and factor VIII elevation in a 36-year-old man

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ABSTRACT

An association has been reported between factor VIII and arterial thrombosis such as ischemic stroke and myocardial infarction. We report a 36-year-old man who had a myocardial infarction despite lacking traditional cardiac risk factors. He developed end-stage heart failure and renal insufficiency necessitating a HeartMate II left ventricular assist device (LVAD). While on the transplant list, he experienced two episodes of LVAD thrombosis 6 months apart, prompting device exchange and escalation of anticoagulation therapy. He eventually underwent a successful heart-kidney transplant before suffering an extensive left lower extremity deep vein thrombosis 6 weeks later. A thrombophilia workup revealed elevated factor VIII activity of 319% (normal range, 50%–150%). He was placed on indefinite anticoagulation with apixaban with no further thrombotic episode in 18 months of follow-up to date.

KEYWORDS Factor VIII; left ventricular assist device; myocardial infarction; thrombophilia; thrombosis

Factor VIII is produced primarily by endothelial cells and is a co-factor in the coagulation cascade. It circulates in plasma noncovalently bound to von Willebrand factor, which protects it from proteolytic inactivation. Exposure to thrombin following endothelial injury causes the dissociation of factor VIII from von Willebrand factor, leading to its activation. Activated factor VIII amplifies thrombin formation and fibrin generation.[1] An increase in factor VIII levels leads to heightened thrombogenicity and is a risk factor for venous thromboembolism (VTE). We report a case of a patient who experienced both arterial and venous thrombotic events before being diagnosed with an elevated factor VIII level.

CASE DESCRIPTION

A nondiabetic, nonsmoking 36-year-old man with a blood pressure of 126/82 mm Hg, body mass index of 31 kg/m^2, total cholesterol of 156 mg/dL, low-density lipoprotein of 84 mg/dL, and hemoglobin A1c of 6.2% presented with acute chest pain and pulseless electrical activity. After successful resuscitation, he was found to have acute 100% occlusion of his left anterior descending artery. The remaining arteries showed no narrowing. He underwent successful thrombectomy followed by drug-eluting stent placement. His course was complicated by acute renal failure and cardiogenic shock requiring temporary intra-aortic balloon pump insertion. After a protracted stay, the patient was discharged. Over the next 4 months, he had multiple hospitalizations for heart failure, ultimately leading to implantation of a HeartMate II ventricular assist device (LVAD) as a bridge to transplant. He was discharged on aspirin 81 mg daily and warfarin to maintain an international normalized ratio of 2.0 to 3.0.

A year later, he developed pump thrombosis in the setting of Neisseria bacteremia and was treated with antibiotics and LVAD exchange. Aspirin was increased to 325 mg daily and his international normalized ratio goal was increased to 2.5 to 3.5. After 6 months, he had a second episode of pump thrombosis without an associated infection. Chest computed

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tomography showed no evidence of cannula malposition or obstruction. He underwent another LVAD exchange. Dipyridamole was added to his full-dose aspirin and warfarin. Four years later, he underwent a combined heart-kidney transplant and was discharged on aspirin 81 mg daily. Six weeks posttransplant he developed acute left lower extremity swelling and developed deep vein thrombosis of the left common femoral, femoral, popliteal, and posterior tibial veins requiring thrombolysis with thrombectomy.

Routine blood work, coagulation studies, and platelet serotonin-release assay testing were unremarkable. Thrombophilia workup did not show any factor V Leiden or prothrombin gene mutation. Protein C, Protein S, antithrombin, von Willebrand factor, and anti-phospholipid antibody levels were normal. However, factor VIII activity was elevated at 319% (normal range, 50%–150%). He was discharged on apixaban and aspirin 81 mg daily. He continues to do well at 18 months posttransplant with no further thrombotic episodes.

DISCUSSION

Elevated factor VIII levels are seen in patients with chronic inflammatory conditions, liver disease, malignancy, renal disease, hyperthyroidism, and intravascular hemolysis. Levels are higher in patients with obesity, diabetes, and hypertriglyceridemia and also increase with age, pregnancy, and after surgery.[2]

Factor VIII levels display significant interindividual variability, with elevated levels found in 11% of the general population.[3] This variability is likely due to environmental factors, but is also genetically determined. Population studies have shown higher levels in African Americans and patients with non-O blood type.[4] Although no polymorphism in the factor VIII gene has been found, genome-wide association studies have identified several genetic foci that may be involved in factor VIII regulation.[5] Factor VIII is an independent risk factor for VTE. In the Leiden thrombophilia study, patients with factor VIII:C $\geq$ 150 IU/dL were found to have an almost 5-fold higher risk of VTE.[3] Moreover, factor VIII levels are predictive of VTE recurrence in a dose-dependent fashion in patients with factor VIII:C $>$ 200 IU/dL.[6]

While the link between factor VIII elevation and VTE is well recognized, studies have also found an association between factor VIII and arterial thrombosis, with suspicion of higher levels of factor VIII leading to an increased incidence of coronary heart disease.[7] After adjusting for traditional risk factors, this association was eliminated, leading the authors to postulate that traditional cardiac risk factors likely exert their effects through elevations of hemostatic factors such as factor VIII.[8]

Increased factor VIII:C levels have been reported in 72.4% of patients with ischemic strokes without vascular risk factors and deemed to be cryptogenic.[9] Those with elevated levels also had a higher incidence of recurrent in-hospital thrombotic events.[10] Myocardial infarctions occurring in individuals with raised factor VIII levels have been recently reported.[11,12] Similar to our case, these patients are young (<45 years old) without significant cardiac risk factors. Our case is unusual in that in addition to myocardial infarction, there were two episodes of LVAD thrombosis. Although LVAD thrombosis may occur in the setting of subtherapeutic anticoagulation or cannula malpositioning, these were not present in our case. We conclude that our patient's recurrent thrombotic events were due to thrombophilia from elevated factor VIII levels.

The mechanism by which raised factor VIII levels increase thrombogenicity remains uncertain. Studies have found that patients with high factor VIII:C and VTE were more likely to have increased levels of prothrombin fragments as well as thrombin-antithrombin complex compared to controls, indicating a higher rate of basal thrombin generation.[1,13] Our case is limited by the reliability of a single point measurement of factor VIII:C drawn right after his deep vein thrombosis was diagnosed. However, O'Donnell et al found that of 35 patients with confirmed VTE disease, 94% had persistent elevations at a median of 8 months with no significant difference in baseline and follow-up values.[14] Even after adjusting for C-reactive protein, high factor VIII levels increased thrombosis risk by 6-fold.[15] This suggests that elevations in general are not caused by acute phase reactions and that there is likely a causal relationship with thrombosis.

Therefore, in the absence of significant prior cardiovascular risk or history or proinflammatory conditions, all potential LVAD candidates, including those with mechanical circulatory support in a chronic stetting who have unexplained thromboses, should undergo thrombophilia workup. The incidence of pump thrombosis, stroke, and other manifestations of coagulopathy has fallen with third-generation pumps but the risk is not zero. We believe that the additional cost of performing these tests in the right clinical setting is more than justified.

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